Uncertainty analysis as essential step in the establishment of the dynamic Design Space of primary drying during freeze-drying - DTU Orbit (09/11/2017)

Uncertainty analysis as essential step in the establishment of the dynamic Design Space of primary drying during freeze-drying

Large molecules, such as biopharmaceuticals, are considered the key driver of growth for the pharmaceutical industry. Freeze-drying is the preferred way to stabilise these products when needed. However, it is an expensive, inefficient, time- and energy-consuming process. During freeze-drying, there are only two main process variables to be set, i.e. the shelf temperature and the chamber pressure, however preferably in a dynamic way. This manuscript focuses on the essential use of uncertainty analysis for the determination and experimental verification of the dynamic primary drying Design Space for pharmaceutical freeze-drying. Traditionally, the chamber pressure and shelf temperature are kept constant during primary drying, leading to less optimal process conditions. In this paper it is demonstrated how a mechanistic model of the primary drying step gives the opportunity to determine the optimal dynamic values for both process variables during processing, resulting in a dynamic Design Space with a well-known risk of failure. This allows running the primary drying process step as time efficient as possible, hereby guaranteeing that the temperature at the sublimation front does not exceed the collapse temperature. The Design Space is the multidimensional combination and interaction of input variables and process parameters leading to the expected product specifications with a controlled (i.e., high) probability. Therefore, inclusion of parameter uncertainty is an essential part in the definition of the Design Space, although it is often neglected. To quantitatively assess the inherent uncertainty on the parameters of the mechanistic model, an uncertainty analysis was performed to establish the borders of the dynamic Design Space, i.e. a time-varying shelf temperature and chamber pressure, associated with a specific risk of failure. A risk of failure acceptance level of 0.01%, i.e. a 'zero-failure' situation, results in an increased primary drying process time compared to the deterministic dynamic Design Space; however, the risk of failure is under control. Experimental verification revealed that only a risk of failure acceptance level of 0.01% yielded a guaranteed zero-defect quality end-product. The computed process settings with a risk of failure acceptance level of 0.01% resulted in a decrease of more than half of the primary drying time in comparison with a regular, conservative cycle with fixed settings. (C) 2016 Published by Elsevier B.V.

General information

State: Published
Organisations: Department of Chemical and Biochemical Engineering, CAPEC-PROCESS, Ghent University
Authors: Mortier, S. T. F. C. (Ekstern), Van Bockstal, P. (Ekstern), Corver, J. (Ekstern), Nopens, I. (Ekstern), Gernaey, K. (Intern), De Beer, T. (Ekstern)
Pages: 71-83
Publication date: 2016
Main Research Area: Technical/natural sciences

Publication information

Journal: European Journal of Pharmaceutics and Biopharmaceutics
Volume: 103
ISSN (Print): 0939-6411
Ratings:
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.49 SJR 1.366 SNIP 1.409
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.414 SNIP 1.496 CiteScore 4.37
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.469 SNIP 1.586 CiteScore 4.44
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.558 SNIP 1.706 CiteScore 4.64
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.976 SNIP 1.933 CiteScore 5.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2

Scopus rating (2011): SJR 1.794 SNIP 1.887 CiteScore 4.77
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.948 SNIP 1.933
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.514 SNIP 1.571
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 1.315 SNIP 1.794
Scopus rating (2007): SJR 1.502 SNIP 1.917
Scopus rating (2006): SJR 1.307 SNIP 1.619
Scopus rating (2005): SJR 1.062 SNIP 1.47
Scopus rating (2004): SJR 0.898 SNIP 1.264
Scopus rating (2003): SJR 1.125 SNIP 1.614
Scopus rating (2002): SJR 1.164 SNIP 1.377
Scopus rating (2001): SJR 0.83 SNIP 1.123
Scopus rating (2000): SJR 0.61 SNIP 0.799
Scopus rating (1999): SJR 0.499 SNIP 0.825
Original language: English
Freeze-drying, Mathematical modelling, Uncertainty analysis, Dynamic Design Space, Biotechnology
DOIs:
10.1016/j.ejpb.2016.03.015
Source: FindIt
Source-ID: 2302938447
Publication: Research - peer-review › Journal article – Annual report year: 2016